Case Report

ZAP70 Related Severe Combined Immunodeficiency Initially Diagnosed as Incomplete (Atypical) Kawasaki Disease

Andrew Alexander, MD; Monika Pilichowska, MD*

Department of Pathology and Laboratory Medicine, Tufts Medical Center, 800 Washington Street, Boston, MA

ZAP70-related severe combined immunodeficiency (SCID) is a defect of the immune system characterized by absent or extremely low CD8+ T-cells and abnormal T-cell receptor signaling. This form of SCID is relatively rare with about 20 cases currently described in the literature and typically presents in infancy with recurrent opportunistic infections, failure to thrive, and gastrointestinal symptoms. This report describes a case of ZAP70-related SCID that was initially diagnosed as incomplete (atypical) Kawasaki disease. A 7-month-old infant presented with two weeks of fever, leukocytosis (33.5 K/µL) and anemia. No infectious etiology was identified and clinical presentation, along with laboratory work-up, suggested incomplete Kawasaki disease. He was treated with a single infusion of IVIG and 72 hours of high dose aspirin with resolution of fever. Seven months later, he presented again with three weeks of fever, persistent leukocytosis, failure to thrive and varicella infection following vaccination. During hospital admission, flow cytometric analysis was conducted to characterize atypical lymphocytes present in peripheral blood. The results revealed nearly absent CD8+ T-cells with a CD4+/CD8+ ratio of 40:1. Subsequent studies demonstrated the absence of ZAP70 expression on T-cells and NK-cells by flow cytometry. Additional testing revealed markedly decreased to absent CD45+ total lymphocyte proliferative response to mitogens and antigens. The patient was diagnosed with ZAP70-related SCID and was referred for further evaluation and bone marrow transplantation. He is currently doing well, apart from minor GVHD, 2 years post-transplant.

[N A J Med Sci. 2017;10(1):29-31. **DOI:** *10.7156/najms.20171001029]*

Key Words: *severe combined immunodeficiency (SCID), ZAP70, Kawasaki disease*

INTRODUCTION

Severe combined immune deficiency (SCID) encompasses a spectrum of disease states characterized by depleted or dysfunctional T-cells, B-cells, and NK cells. These defects severely hamper adaptive immune response and can result in diminished serum immunoglobulins. Although the genetic abnormalities underlying SCID are heterogeneous, the clinical presentation typically involves opportunistic infections and failure to thrive during infancy.[1] Mutations involving the zeta chain associated protein kinase 70 (ZAP70), which is involved in T-cell receptor(TCR) signaling, can induce a SCID state through disruptions in T-cell differentiation and function. The mutations are characterized by $CD8^+$ T cell lymphopenia and anergic $CD4^+$ T cells that fail to respond to mitogen stimulation.[2,3,4] The prevalence of ZAP70 mutations is relatively low, with about 20 affected individuals identified/reported. These individuals represent a diagnostic challenge due to the clinical heterogeneity of their presentation.[1,5]

Received: 06/29/2015; Revised: 07/15/2015; Accepted: 07/22/2015
***Corresponding Author:** Department of Pathology and Laboratory Medicine, Tufts Medical Center, 800 Washington Street, Boston, MA 02111. (Email: mpilichowska@tuftsmedicalcenter.org)

We report a case of a 7-month-old infant who presented with recurrent fevers, skin rash, and gastrointestinal symptoms (diarrhea). He was initially treated for incomplete (atypical) Kawasaki disease before the diagnosis of SCID with underlying ZAP70 deficiency was made. This case report demonstrated the value of flow cytometric analysis performed on peripheral blood as a diagnostic tool in this rare condition. In this case, timely diagnosis resulted in the initiation of appropriate treatment early in the course of the disease. This report also serves as a teaching case in recognizing SCID and suspecting a ZAP70 defect as an underlying cause.

CASE PRESENTATION

The patient was a Caucasian male born at term with a normal birth weight following an uneventful pregnancy. There were neither known maternal risk factors nor significant family medical history. He was developing normally until 7 months of age when he presented with two weeks of cough, diarrhea, vomiting, and fevers up to 40°C. Initial laboratory evaluation revealed elevated WBC count (33.5 K/µL) and C-reactive protein (CRP) (132 mg/L) with chest X-ray features suggestive of viral infection [Table 1]. On hospital day 3

infectious causes were ruled out and the symptoms, which included submental lymphadenopathy and erythematous feet in addition to persistent fever and elevated CRP, were interpreted as incomplete Kawasaki disease. Given this diagnosis, treatment with a single dose of IVIG in conjunction with 72 hours of high dose aspirin was initiated. Further workup with echocardiogram failed to demonstrate any pathology involving the coronary arteries. By hospital day 5, the patient's fevers had subsided and laboratory values were normalizing, resulting in hospital discharge.

Shortly thereafter, the patient experienced persistent leukocytosis (WBC 19.2 K/µL), night time cough, and perioral erythema without fever or signs of infection. He also developed a varicella infection, immediately following vaccination, that necessitated a 5 day course of acyclovir. He was admitted again at 17 months with acute otitis media, three weeks of fever and a pruritic, erythematous rash on the face and extremities. Immunoglobulin levels were within normal limits aside from a mildly depressed IgM. He received a 600 mg/kg dose of IVIG; on this admission laboratory evaluation of the peripheral blood smear revealed atypical lymphocytes **(Figure 1)**. Flow cytometric evaluation of peripheral blood was performed and demonstrated a markedly reduced CD8 count and a significantly increased CD4:CD8 ratio of 40:1. Based on this finding ZAP70 deficiency was suspected. Subsequent testing including mitogen stimulation (conducted at Cincinnati Children's Hospital) revealed markedly decreased response to phytohemagglutinin, concanavalin A and pokeweed mitogens. Immunologic studies revealed that ZAP70 expression was not detected in the patient's T or NK cell populations by flow cytometry. These findings were indicative of ZAP70 deficiency, and the patient was transferred to Boston Children's Hospital for hematopoietic stem cell transplantation (HSCT). He is currently doing well, apart from mild GVHD, 2 years post-transplant.

Table 1. Laboratory values during initial presentation at 7 months old.

WBC (6.2-14.5) k/µL	33.5	Blood urea nitrogen (5-17) mg/dL	3
RBC (4.1-5.0) M/µL	3.45	Creatinine (0.57-1.3) mg/dL	0.33
HGB (10.3-12.4) g/dL	9.0	Sodium (135-145) meq/L	141
HCT (30.9-37.0) %	26.6	Potassium (3.6-5.1) meq/L	3.0
Platelets (219-452) k/µL	288	Chloride (98-110) meq/L	109
MCV (70.5-81.2) FL	77.1	Aspartate Aminotranferase (20-60) IU/L	34
RDW (13.1-15.6) %	18.0	Lactate Dehydrogenase (120-220) IU/L	459
Segmented Neutrophil %	55	Alkaline Phosphatase (145-320) IU/L	116
Lymphocyte %	41	Bilirubin total (0.2-1.1) mg/dL	0.4
Monocyte %	3	C-Reactive Protein (CRP) (0.00-7.48) mg/L	132.30
Eosinophil %	0	Iron (49-181) µg/dL	13
Basophil %	0	% Iron Saturation (25-72) %	5
Band Neutrophil %	1	Ferritin (22-227) ng/mL	732
Reticulocyte Count (08.-2.0) %	0.6	Transferrin (181-331) mg/dL	190

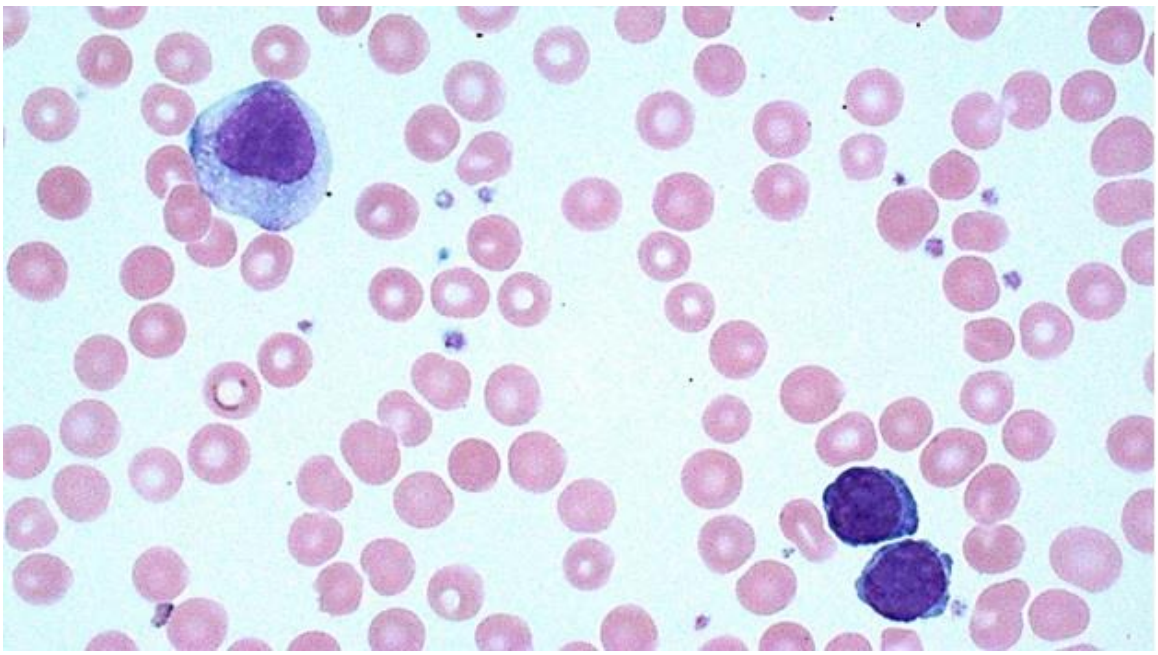

Figure 1. Peripheral blood findings in the patient with ZAP70 related SCID. Atypical lymphocyte is noted (arrow). Wright-Giemsa stain at x1000 magnification.

DISCUSSION

Unlike other forms of SCID, ZAP70 deficiency does not present with thymic dysfunction. While ZAP70 is critical for $CD8^+$ T-cell selection and peripheral $CD4^+$ T-cell function, its absence does not prevent $CD4^+$ T-cell section in the thymus. This results in low to absent $CD8^+$ T-cell counts and normal to increased $CD4^+$ T-cell counts. The exact mechanism by which ZAP70 deficiency interferes with positive selection of $CD8^+$ thymocytes remains unclear. Spleen tyrosine kinase (SyK), which is down-regulated in mature peripheral T-cells, is thought to compensate for ZAP70 signaling in thymocyte $CD4^+$ lineage selection. Peripheral $CD4^+$ T-cell dysfunction manifests as a failure to proliferate or produce IL-2 in response to stimulation by mitogens. This occurs due to impaired ZAP70 mediated signaling downstream of the T-cell receptor.[6]

The initial presentation of this patient's ZAP70 deficiency highlights the clinical heterogeneity present within ZAP70 related SCID that other authors have previously commented on.[1,2] Among the clinical presentations previously reported include a classic SCID presentation, Omenn phenotype following BCG vaccination, disseminated mycobacterial infections and cerebral infarction.[7] The patient in this study did not present with classic SCID symptoms. Instead, the defining features of the patient's initial presentation were persistent leukocytosis, intractable fever, lymphadenopathy and rash. These findings, in conjunction with a lack of a definitive infectious etiology, lead to the initial diagnosis of incomplete Kawasaki disease.

Kawasaki disease is a medium sized vessel vasculitis that manifests as an acute febrile illness. Due to a tendency to involve coronary arteries, cardiac sequelae such as coronary artery aneurysms are associated with the disease. The diagnosis is based on clinical criteria. The most common symptoms include an uncontrollable fever lasting at least 4 days in conjunction with four principle criteria including cervical lymphadenopathy, conjunctival injection, polymorphous exanthema, and changes to the oral cavity and extremities. Incomplete Kawasaki disease encompasses a subset of patients that display some of the classical symptoms of Kawasaki disease without meeting enough of the principle criteria to be diagnosed with Kawasaki disease.[8] The diagnosis of incomplete Kawasaki disease is not specific and can represent the initial manifestation of congenital immunodeficiency disorders such as ZAP70 deficiency. Complete immunologic workup can be helpful, but it is usually not performed as a part of initial evaluation. Flow cytometry, on the contrary can easily identify major immune cell subsets. In our case, the absence of CD8 cells lead to suspicion of ZAP70 deficiency and to a complete immunodeficiency workup. Due to the rarity of ZAP70 deficiency, this entity is rarely suspected. However, immunodeficiency needs to be suspected with recurrent infections where a definitive infectious etiology is not identified. This case highlights the clinical heterogeneity of ZAP70 deficiency at initial presentation and illustrates utility of routine flow cytometric analysis as a diagnostic tool to investigate the presence of ZAP70 deficiency.

CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

REFERENCES

1. Turul T, Tezcan I, Artac H, et al. Clinical heterogeneity can hamper the diagnosis of patients with ZAP70 deficiency. Eur J Pediatr. 2009;168:87-93.
2. Esenboga S, Ayvaz DC, Cetinkaya PG, Burg M, Tezcan I. An infant with ZAP-70 deficiency with disseminated mycobacterial disease. J Clin Immunol. 2016;36:103-106.
3. Elder M, Lin D, Clever J, et al. Human Severe Combined Immunodeficiency Due to a Defect in Zap-70, a T Cell Tyrosine Kinase. Science. 1994;264:1596-1598.
4. Karaca E, Karakoc-Aydiner E, Bayrak O, et al. Identification of a novel mutation in *ZAP70* and prenatal diagnosis in a Turkish family with severe combined immunodeficiency disorder. Gene. 2013;512:189-193.
5. National Institutes of Health. Zap70-related severe combined immunodeficiency. https://ghr.nlm.nih.gov/condition/zap70-related-severe-combined-immunodeficiency#statistics. November 1, 2016.
6. Au-Yeung B, Deindl S, Hsu L, et al. The structure, regulation, and function of ZAP-70. Immunol Rev. 2009;228:41-57.
7. Haluk Akar H, Patiroglu T, Akyildiz BN, et al. Silent brain infarcts in two patients with zeta chain-associated protein 70 kDa (ZAP70) deficiency. Clin Immunol. 2015;158:88-91.
8. Son MB, Newburger JW. Kawasaki disease. Pediatr Rev. 2013;34:151-161.